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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/061,417	04/16/1998	ERIC N. OLSON	UTSD:548	1649

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/061,417	Applicant(s) OLSON ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-8 and 10-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 4, 9 are being examined.

This application contains claims drawn to an invention nonelected in Paper No.14. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9 pertaining to lack of enablement for a method of treating hypertrophy remains for reasons already of record in paper No.18.

Applicant argues that although the use of NF-AT3 inhibitors to treat hypertrophy is not well-known, but the information provided in the specification, coupled with what was known prior to this invention, would allow one of skill in the art to practice the invention. Applicant further argues that the Examiner's criticism almost seems to rise to the level of requiring a working model, and according to MPEP 2164.02, Applicant

needs not have actually reduced the invention to practice prior to filing. Applicant further argues that Examples 6-9 in the specification show *in vivo* proof that use of NF-AT3 inhibitors can be a method for treating hypertrophy.

Concerning the Examiner's statement that the transfected cells and transgenic mice are not representative of what would be found in human subjects, Applicant submits an Affidavit of Dr. Rick Gorczynski, regarding the validity of the transfection model and transgenic mouse model, and recites Ritter et al, which teaches that NF-AT2 is in a dephosphorylated and therefore more active form in hypertrophic heart, as compared to normal heart. Applicant asserts that these results provide *in vivo* evidence from a human clinical setting, albeit indirect, that there is altered NF-AT phosphorylation state in hypertrophied myocardium. It further validates the notion of targeting NF-ATs therapeutically to combat hypertrophy by interfering with the NF-AT transcriptional cascade.

Concerning the issues of transfected cells, Applicant recites the references by Molkentin et al, JBC, 2000, and Olson et al, stating that based on the results of these references, one would recognize that NF-AT3 does indeed interact with GATA-4. Applicant further argues that the review by Molkentin et al, JBC, 2000, states that GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT), recites Molketin et al, Cell, 1998, and Morin et al, 2000, the Gorczynski Declaration, and concludes that the current state of the field of cardiac hypertrophy studies accepts that GATA-4 does indeed interact with NF-AT3.

Applicant recites the case law *In re Robins*, stating that this rejection goes beyond reasonable requirements for 112. Concerning the Examiner's statement that one would not know how to use the claimed method, using the small single chain antibodies, Applicant asserts that this conclusions is contrary to the holding in *In re Wands*, that so long as there is consideration guidance in the specification, and all of the methods to practice the invention are known, then it would not require undue experimentation to obtain antibodies needed to practice the claimed invention.

The submission of the Gorczynski Declaration, the recitation of MPEP 2164.02, the references by Molketin et al, Cell, 1998, Molkentin et al, JBC, 2000, Olson et al, and Morin et al, and the case law *In re Wands* and *In re Robins* is acknowledged.

It is noted that Molketin and Olson, the main authors of the referred references seem to be the same as the inventors of the instant application. Further, it is noted that Morin et al teach binding of GATA-4 to MEF2 protein *in vitro* and thus the reference by Morin et al is not related to the issue of binding GATA-4 with NF-AT3 *in vivo,* because MEF-2 protein is a different protein than NF-AT4.

Applicant's arguments set forth in paper No.19 have been considered but are not deemed to be persuasive for the following reasons:

Concerning Applicant assertion that the Examiner's criticism almost seems to rise to the level of requiring a working model, and that it is well established that examples are not required to prove enablement, MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In

re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Since little is known in the art about treating hypertrophy, using a small molecule inhibitor that bind to and inactivates NF-AT3, since the specification lacks reasonable amount of guidance or direction on how to make or use the invention, and further since there is overwhelming evidence that treatment of hypertrophy using a small molecule that binds to and inactivates NF-AT3 is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling.

Concerning the disclosures of Example 6-9, contrary to Applicant's assertion, Examples 6-9 clearly do not show any *in vivo* proof that the use of NF-AT3 inhibitors can be a method to treat hypertrophy. Examples 6 and 7 disclose induction of cardiac hypertrophy *in vivo* in transgenic mice having continously activated calcineurin, and activation of various genes *in vivo* by activated calcineurin. Applicant hypothesizes that calcineurin would dephosphorylate NF-AT3 in the cytoplasm of cardiomyocytes, enabling its translocation to the nucleus, where it can interact with GATA-4, resulting in up-regulation of cardiac hypertrophic genes, such as beta-naturietic peptide (BNP)

responsible for hypertrophy (p. 13, first paragraph, and figure 8). Examples 6 and 7 however clearly does not disclose nor shows any *in vivo* proof that NF-AT3 is activated in the hearts of patients having cardiac hypertrophy, and is responsible for up-regulation of cardiac hypertrophic genes via interaction with GATA4 *in vivo* in patients with cardiac hypertrophy and that use of NF-AT3 inhibitors can be a method to treat hypertrophy. Example 8 shows that transgenic mice, which are transfected with a mutant NF-AT3, which is continously activated, and expressed in the hearts, have cardiac hypertrophy. However, said transgenic mice do not represent a model for cardiac hypertrophy for human. Applicant has not shown that NF-AT3 is continously activated in the hearts of patients having cardiac hypertrophy, and is responsible for up-regulation of cardiac hypertrophic genes via interaction with GATA4 *in vivo* in patients with cardiac hypertrophy. Further, although Ritter et al teach that NF-AT2 is dephosphorylated in hypertrophic heart, it is not necessarily that NF-AT3, although belonging to the same family NF-AT, would be dephosphorylated, because different genes are independently regulated. Further, even if NF-AT3 is dephosphorylated in hypertrophic heart and although dephosphorylation would translocate NF-AT-3, one could not predict that dephosphorylation would be sufficient to activate NF-AT3, which in turn would bind to GATA4 *in vivo* in patients with cardiac hypertrophy, and responsible for up-regulation of cardiac hypertrophic genes. Example 9 discloses prevention of cardiac hypertrophy with CsA in calcineurin transgenic mice. This example only discloses inhibition of calcineurin *in vivo* in calcineurin transgenic mice, and not treating of hypertrophy in patients with cardiac hypertrophy with an inhibitor of NF-AT-3. Further, it is questionable

that the transgenic mice is representative of patients with cardiac hypertrophy, because the transgene calcineurin is constitutively active, i.e. continuously active, which is not the same as the conditions of patients with cardiac hypertrophy.

Further, although Molketin et al, 1998, 2000 and Olson et al, 2000, teach that NF-AT3 does interact with GATA-4 *in vitro*, one could not predict that NF-AT3 interacts with GATA-4 *in vivo,* and causing cardiac hypertrophy, because of the following reasons: The interaction between NF-AT3 and GATA4 as shown in example 2 of the specification, and disclosed in Molkentin et al, Cell, 1998, page 216, is only from mouse embryo libraries, which are not cardiomyocyte cells, and one cannot predict that there is the same interaction between NF-AT3 and GATA4 in cardiomyocyte cells . Further, although BNP promoter is up-regulated in the presence of GATA4, NF-AT3 and calcineurin in cardiomyocyte cells, as disclosed in example 4 of the specification and Molkentin et al, Cell, 1998, pages 218-219, the cardiomyocyte cells are however transfected with GATA4, NF-AT3, the artifial condition of overexpression and overabundance of which could effect the distribution and thus forced interaction between GATA4 and NF-AT3. Further, the transfected calcineurin is in a mutant form, which is constitutively, i.e. continously, active. Thus the conditions of the transfected cells would not be even remotely similar conditions as in hypertrophic cardiomyocyte cells *in vivo.* Further, one could not apply *in vitro* conditions to *in vivo* conditions because of the following reasons: 1) cell culture artifacts are well known in the art, and 2) characteristics of cultured cell lines generally differ significantly from the characteristics of a primary cell, wherein specific cell-cell interactions and homeostatic

regulation is lost in tissue culture, as taught by Freshney (of record). Further, Thum T et al, 2001, of record, teach that the levels of expression of target genes of GATA-4 in cells in cultures increase as compared to those from freshly isolated cells, thus clearly indicating that *in vitro* cells could not represent *in vivo* cells, and that it is unpredictable that the level of GATA-4, which is well known in the art to interact with several transcriptional factors, is adequate in patients with cardiac hypertrophy for interaction with NF-AT3, for up-regulating cardiac hypertrophic genes.

Moreover, as indicated by Olson et al (BioEssays, 2000, 22: 510-519, recited by Applicant), the specific genes that act directly as the effectors of hypertrophy have not been identified, and so far, specific genes that have been shown most clearly to respond to hypertrophic signaling pathways appear to represent only markers of the process (p.516, second column, 4th paragraph). Thus it is not even clear which genes that act directly as the effectors of hypertrophy would be under the control of NFAT-3.

Thus, one cannot predict that NF-ATF-3 is continuously activated in the hearts of patients having cardiac hypertrophy, and is responsible for up-regulation of cardiac hypertrophic genes *in vivo* via binding with GATA4 *in vivo*. Further, even NF-ATF-3 is responsible for up-regulation of cardiac hypertrophic genes *in vivo*, one cannot predict that inhibition of NF-AT3 *in vivo* would abolish the up-regulation of cardiac hypertrophic gene, because homeostatic regulation is well known in the art, *supra*, and as shown in NFAT1-deficient mice, targeting of NFAT-1 does not render the mice immunocompetent, and the cytokine genes that are known to be under the control of

NFAT1 are not effected in NFAT1-deficient mice (Rao A et al, 1997, Ann Rev Immunol, 15: 707-47, especially pages 736-737).

Further, there is no teaching in the specification of how to make and use the claimed small inhibitors of NF-ATF-3. Concerning how to make single chain antibodies that are antagonists of NF-ATF-3, although the specification discloses that the Rel homology domain of NF-AT3 is sufficient for the binding of NF-AT3 to GATA4, it is unpredictable that said region is necessary for the binding of NF-AT3 to GATA4. In other words, the epitope of the claimed antagonist single chain antibodies against NF-AT3 is not known. As discussed in the previous Office action, there is no teaching of the linear or three dimensional structures of the epitope for the claimed antibodies, as defined by Herbert et al (of record), wherein defining the epitope is not as easy as it seems, as taught by Greenspan et al (of record). Therefore, it would be random experimentation to make the claimed single antibodies, and it would be undue experimentation for one skill in the art to make and use the claimed single antibodies specific for NF-ATF-3 for treating hypertrophy.

Concerning the small DTC's, which are not taught in the specification, it is not clear whether DTC's actually bind to NF-AT3, which is the limitation of claims 4 and 9. Moreover, DTC's have other effects besides inhibition of NFATp, such as potent inhibition of NF-κB activation (Martinez-Martinez et al, recited by Applicant in previous response), which is notoriously well known in the art to be involved in regulation of numerous cell function, and thus the effects of DTC's to patients are unpredictable. Further, DTC's has been shown by Martinez-Martinez et al as an inhibitor of NFAT only

in vitro and in T cells. It is well known in the art that one could not apply *in vitro* conditions to *in vivo* conditions, due to cell culture artifacts, and significant differences in characteristics of cultured cell lines and a primary cell, wherein specific cell-cell interactions and homeostatic regulation is lost in tissue culture, as taught by Freshney and Thum et al (of record). Further, although DTC's is an inhibitor of NFAT in T cells, it is unpredictable that DTC's is active in cardiomyocytes, because different cells are have different properties and characteristics in responding to drugs.

Concerning the use of GATA4 mimetics for treating hypertrophy, the structure of the mimetics is not disclosed by the specification and is not predictable, as discussed in previous Office action, and one would not know how to use the claimed mimetics for treating hypertrophy.

Thus there is overwhelming evidence that treatment of hypertrophy using a small molecule that binds to and inactivates NF-AT3 is unpredictable

In conclusion, although an example is not always required, but in view of the lack of an adequate teaching in the specification of how to make and use the claimed invention, and for the reasons set forth above, and previously, it would have been a burden for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102

Rejection under 35 USC 102 of claim 1 pertaining to anticipation by Haverich et al, or Ried et al, as evidenced by McCaffrey et al, and Martinez-Martinez et al remains for reasons already of record in paper No.18.

Applicant asserts that every element of claim 1 is not found in any of the prior art references. None of the recited references teach treatment of hypertrophy or effects on cardiac structure. Haverich et al, Ried et al only teach the use of CsA for treatment of transplantation disease. They are instead directed towards improving cardiac function in a post-transplant environment.

Applicant's arguments set forth in paper No.19 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that it is notoriously well known in the art that transplanted heart soon develops ventricular hypertrophy.

Thus, although the references do not recite treatment of hypertrophy, however, because the method of the prior art comprises the same method step as claimed in the instant invention using the same composition, i.e. a compound that inhibits the function of NF-AT3, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MINH TAM DAVIS

October 17, 2002